IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Vincent P. Stanton, Jr. Art Unit :
Serial No. : Examiner :
Filed : HEREWITH
Title : THYMIDYLATE SYNTHASE GENE SEQUENCE VARIANCES HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the Title:

Replace the title with the following new title:

-- THYMIDYLATE SYNTHASE GENE SEQUENCE VARIANCES HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE--

In the specification:

Insert the enclosed Sequence Listing into the specification after the Oath and Declaration.

Replace the paragraph beginning at page 1, line 8, with the following new paragraph:

--This application is a divisional of U.S. Application Serial No. 09/658,659, filed September 8, 2000, which is a CIP of Stanton, U.S. Application serial No. 09/596,033, filed June 15, 2000 entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application 09/357,743, filed July 20, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton,

CERTIFICATE OF MAILING BY EXPRESS MAIL

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I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

September 24, 2001
Date of Deposit

Signature

Lisa C Gray
Typed or Printed Name of Person Signing Certificate

U.S. Application Serial No. 09/357,024, filed July 19, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which claims the benefit of Stanton, U.S. Provisional Application 60/093,484, filed July 20, 1998, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which are all hereby incorporated by reference in their entireties including drawings and tables.--

Replace Table 10 beginning at page 171, with the following table:

Table 10

Variance Table

Hugo	GID	OMIM ID	VGX Symbol	Description
	Variance Start	Variance		
U73338	U73338	156570	GEN-69	Methionine Synthase (SEQ ID NO:1)
	194	(-201)C>G	5'	
	284	(-111)C>T	5'	
	1136	742G>A	V248M	
	1252	858C>T	Silent	
	1334	940G>A	D314N	
	1699	1305T>C	Silent	
	3150	2756A>G	D919G	
	3207	2813G>T	S938I	
	3209	2815G>C	G939R	
	5444	5050C>A	3'	
	5551	5157G>A	3'	
	5573	5179C>T	3'	
	5659	5265T>C	3'	
	5678	5284T>C	3'	
	5874	5480C>T	3'	
	5934	5540A>G	3'	
D78586	D78586	114010	GEN-BR	CAD PROTEIN (SEQ ID NO:2)
	3434	3408C>T	Silent	
	4313	4287T>C	Silent	
	4799	4773A>G	Silent	
	5255	5229C>T	Silent	
	5455	5429G>A	R1810Q	

5507	5481T>C	Silent
5810	5784C>T	Silent
6128	6102C>T	Silent
6626	6600C>T	Silent
6686	6660C>T	Silent

U09178 U09178 274270 GEN-HA Dihydropyrimidine Dehydrogenase (SEQ ID NO:3)

166	85T>C	C29R
577	496A>G	M166V
638	557A>G	Y186C
1708	1627A>G	I543V
3432	3351T>C	3'
3682	3601C>T	3'
3730	3649G>A	3'
3925	3844A>G	3'
3937	3856T>C	3'

U19720 U19720 600424 GEN-I1 Folate Transporter (SLC19A1) (SEQ ID NO:4)

175	80G>A	R27H
341	246C>G	Silent
791	696C>T	Silent
1067	972G>A	Silent
1337	1242C>A	Silent
1997	1902T>C	3'
2100	2005^2006insG	3'
2582	2487T>G	3'
2617	2522C>T	3'
2652	2557T>C	3'

U92868 U92868 600424 GEN-LUK Homo sapiens reduced folate carrier (RFC1) gene, exons 1a, 1c and 1b (SEQ ID NO:5)

431	431A>G	Intron
441	441A>G	Intron
498	498C>T	Intron
579	579G>C	Intron
599	599G>C	Intron

X02308 X02308 188350 GEN-KL Thymidylate synthetase (SEQ ID NO:6)

1066	961T>C	3'
1136	1031A>G	3'
1497	1392T>A	3'

D00517 D00517 188350 GEN-LUC Thymidylate synthase, promoter (SEQ ID NO:7)

276	276C>T	Intron
321	321T>C	Intron
452	452G>A	Intron

	457	457^insC	Intron
	491	491C>A	Intron
	533	533T>C	Intron
	624	624A>C	Intron
	639	639A>G	Intron
	655	655T>C	Intron

D00596 D00596 188350 GEN-LUD Homo sapiens gene for thymidylate synthase, exons 1, 2, 3, 4, 5, 6, 7, complete cds (SEQ ID NO:8)

	701	701A>C	Intron
	716	716A>G	Intron
	732	732T>C	Intron
	1293	1293A>G	Intron
	1322	1322C>G	Intron
	1379	1379T>C	Intron
	1590	1590C>T	Intron
	1688	1688C>G	Intron
	2401	2401A>G	Intron
	2429	2429G>A	Intron
	2488	2488C>T	Intron
	2594	2594G>T	Intron
	2618	2618G>A	Intron
	3083	3083G>A	Intron
	3125	3125G>A	Intron
	3212	3212C>T	Intron
	3619	3619T>A	Intron
	3635	3635G>A	Intron
	4256	4256G>A	Intron
	4898	4898A>G	Intron
	5006	5006C>T	Intron
	5062	5062G>A	Intron
	5167	5167G>A	Intron
	11069	11069A>G	Intron
	11238	11238C>T	Intron
	11293	11293T>G	Intron
	11422	11422T>C	Intron
	11686	11686C>T	Intron
	12598	12598T>C	Intron
	13171	13171T>C	Intron
	13298	13298G>A	Intron
	13645	13645T>C	Intron
	13751	13751C>A	Intron
	13782	13782T>C	Intron
	13806	13806T>C	Intron
	13813	13813T>C	Intron

14479	14479A>G	Intron	
14546	14546^insT	Intron	
14585	14585C>T	Intron	
14729	14729G>A	Intron	
14787	14787C>T	Intron	
14795	14795G>A	Intron	
15041	15041T>C	Intron	
15343	15343G>A	Intron	
15449	15449G>A	Intron	
15502	15502G>A	Intron	
15545	15545C>T	Intron	
15589	15589A>G	Intron	
15769	15769C>T	3'	
15839	15839A>G	3'	
16148	16148G>A	3'	
16198	16198T>G	3'	
16202	16202G>T	Intron	

X59618 X59618 180390 GEN-M3 Ribonucleotide reductase M2 polypeptide (SEQ ID NO:9)

128	(-67)G>A	5'
189	(-6)T>G	5'
524	330C>G	Silent
1399	1205T>A	3'
1464	1270G>A	3'
1636	1442C>T	3'
1738	1544C>T	3'
2259	2065T>C	3'

S72487 S72487 131222 GEN-3LD Thymidine phosphorylase, partial (SEQ ID NO:10)

183	19G>A	D7N
483	319C>T	3'
601	437G>C	3'
1299	1135G>A	3'

M58602 M58602 131222 GEN-LUB Thymidine phosphorylase, promoter and genomic (SEQ ID NO:11)

124	124C>T	3'
439	439G>A	3'
1044	1044^insCT	3'
1331	1331G>A	3'
1977	1977G>A	Intron
2149	2149G>A	Intron
2467	2467A>G	Intron
2634	2634C>G	Intron
2975	2975G>A	Intron
3116	3116G>T	Intron

3255 3255A>C Intron
3344 3344T>C Intron
4051 4051C>A Intron
4782 4782G>A Intron
5022 5022T>C Intron
5266 5266G>A Intron
5285 5285C>G Intron
5438 5438T>A Intron
5482 5482C>T Intron
5629 5629G>A Intron
5648 5648C>T Intron
5731 5731G>A Intron

M98045 M98045 136510 GEN-4C3 Homo sapiens folylpolyglutamate synthetase mRNA, complete cds (SEQ ID NO:12)

802 732C>T Silent
1747 1677G>T 3'
1900 1830T>C 3'

U24253 U24253 136510 GEN-LUE Human folylpolyglutamate synthetase (FPGS) gene, exons 5-11, and partial cds (SEQ ID NO:13)

1424 1424C>A Intron
1649 1649G>A Intron
2554 2554A>G Intron

U24252 U24252 136510 GEN-LUF Folylpolyglutamate synthetase, promoter and exons 1-4 (SEQ ID NO:14)

263 263A>G Intron
266 266G>T Intron
527 527C>G Intron
1037 1037A>G 5'
1139 1139G>A Intron
1217 1217C>T Intron
1647 1647C>T Intron
1955 1955G>A Intron
2017 2017G>A Intron
2037 2037G>A Intron
2189 2189A>G Intron
2282 2282C>T Intron
2309 2309A>G Intron

U09806 U09806 236250 GEN-4FZ Human methylenetetrahydrofolate reductase mRNA, partial cds (SEQ ID NO:15)

120 120T>C Silent
464 464T>G M155R
519 519C>T Silent

	668	668C>T	A223V	
	1059	1059T>C	Silent	
	1289	1289C>A	3'	
	1308	1308T>C	3'	
	1784	1784G>A	3'	
AF061655	AF061655	123920 GEN-LUJ	Cytidine	
deaminase, promoter (SEQ ID NO:16)				
	575	575T>C	Intron	
	648	648T>C	Intron	
	771	771G>C	Intron	
	883	883G>A	Intron	
	941	941^insC	5'	
	1051	1051A>C	K27Q	

In the claims

Cancel claim 1-16.
Add new claims 17 - 49

--17. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:6, the probe comprising at least one of:
(a) nucleotide 1066 wherein N is C;
(b) nucleotide 1136 wherein N is G;
(c) nucleotide 1497 wherein N is A;
or the complement thereof.

18. The isolated nucleic acid probe of claim 17 comprising at least two of:
(a) nucleotide 1066 wherein N is C;
(b) nucleotide 1136 wherein N is G;
(c) nucleotide 1497 wherein N is A;
or the complement thereof.

19 The probe of claim 17 comprising no more than 500 contiguous nucleotides of SEQ ID NO:6.

20. The probe of claim 17 comprising no more than 200 contiguous nucleotides of SEQ ID NO:6.

21. The probe of claim 17 comprising no more than 100 contiguous nucleotides of SEQ ID NO:6.

22. The probe of claim 17 comprising no more than 50 contiguous nucleotides of SEQ ID NO:6.

23. The probe of claim 17 comprising DNA.

24. The probe of claim 17 comprising a peptide nucleic acid.

25. The probe of claim 17 further comprising a detectable label.

26. The probe of claim 25 wherein the detectable label is a fluorescent label.

27. A method comprising:

(a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient;

(b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:6, the probe comprising at least one of:

(i) nucleotide 1066 wherein N is C;
(ii) nucleotide 1136 wherein N is G;
(iii) nucleotide 1497 wherein N is A;

or the complement thereof; and

(c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.

28. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:7, the probe comprising at least one of:

(a) nucleotide 276 wherein N is T;
(b) nucleotide 321 wherein N is C;
(c) nucleotide 452 wherein N is A;
(d) C is inserted after nucleotide 457;
(e) nucleotide 491 wherein N is A;
(f) nucleotide 533 wherein N is C;
(g) nucleotide 624 wherein N is C;
(h) nucleotide 639 wherein N is G;
(i) nucleotide 655 wherein N is C;

or the complement thereof.

29. The isolated nucleic acid probe of claim 28 comprising at least two of:

(a) nucleotide 276 wherein N is T;
(b) nucleotide 321 wherein N is C;
(c) nucleotide 452 wherein N is A;
(d) C is inserted after nucleotide 457;
(e) nucleotide 491 wherein N is A;
(f) nucleotide 533 wherein N is C;
(g) nucleotide 624 wherein N is C;
(h) nucleotide 639 wherein N is G;
(i) nucleotide 655 wherein N is C;

or the complement thereof.

30. The probe of claim 28 comprising no more than 500 contiguous nucleotides of SEQ ID NO:7.

31. The probe of claim 28 comprising no more than 200 contiguous nucleotides of SEQ ID NO:7.

32. The probe of claim 28 comprising no more than 100 contiguous nucleotides of SEQ ID NO:7.

33. The probe of claim 28 comprising no more than 50 contiguous nucleotides of SEQ ID NO:7.

34. The probe of claim 28 comprising DNA.

35. The probe of claim 28 comprising a peptide nucleic acid.

36. The probe of claim 28 further comprising a detectable label.

37. The probe of claim 36 wherein the detectable label is a fluorescent label.

38. A method comprising:

(a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient;

(b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:7, the probe comprising at least one of:

(i) nucleotide 276 wherein N is T;
(ii) nucleotide 321 wherein N is C;
(iii) nucleotide 452 wherein N is A;
(iv) C is inserted after nucleotide 457;
(v) nucleotide 491 wherein N is A;
(vi) nucleotide 533 wherein N is C;
(vii) nucleotide 624 wherein N is C;
(viii) nucleotide 639 wherein N is G;
(ixi) nucleotide 655 wherein N is C;

or the complement thereof; and

(c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.

39. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:8, the probe comprising at least one of:

(a) nucleotide 701 wherein N is C;
(b) nucleotide 716 wherein N is G;

(c) nucleotide 732 wherein N is C;
(d) nucleotide 1293 wherein N is G;
(e) nucleotide 1322 wherein N is G;
(f) nucleotide 1379 wherein N is C;
(g) nucleotide 1590 wherein N is T;
(h) nucleotide 1688 wherein N is G;
(i) nucleotide 2401 wherein N is G;
(j) nucleotide 2429 wherein N is A;
(k) nucleotide 2488 wherein N is T;
(l) nucleotide 2594 wherein N is T;
(m) nucleotide 2618 wherein N is A;
(n) nucleotide 3083 wherein N is A;
(o) nucleotide 3125 wherein N is A;
(p) nucleotide 3212 wherein N is T;
(q) nucleotide 3619 wherein N is A;
(r) nucleotide 3635 wherein N is A;
(s) nucleotide 4256 wherein N is A;
(t) nucleotide 4898 wherein N is G;
(u) nucleotide 5006 wherein N is T;
(v) nucleotide 5062 wherein N is A;
(w) nucleotide 5167 wherein N is A;
(x) nucleotide 11069 wherein N is G;
(y) nucleotide 11238 wherein N is T;
(z) nucleotide 11293 wherein N is G;
(aa) nucleotide 11422 wherein N is C;
(bb) nucleotide 11686 wherein N is T;
(cc) nucleotide 12598 wherein N is C;
(dd) nucleotide 13171 wherein N is C;
(ee) nucleotide 13298 wherein N is A;
(ff) nucleotide 13645 wherein N is C;
(gg) nucleotide 13751 wherein N is A;
(hh) nucleotide 13782 wherein N is C;
(ii) nucleotide 13806 wherein N is C;
(jj) nucleotide 13813 wherein N is C;
(kk) nucleotide 14479 wherein N is G;
(ll) T is inserted after nucleotide 14546;
(mm) nucleotide 14585 wherein N is T;
(nn) nucleotide 14729 wherein N is A;
(oo) nucleotide 14787 wherein N is T;
(pp) nucleotide 14795 wherein N is A;
(qq) nucleotide 15041 wherein N is C;
(rr) nucleotide 15343 wherein N is A;
(ss) nucleotide 15449 wherein N is A;
(tt) nucleotide 15502 wherein N is A;

(uu) nucleotide 15545 wherein N is T;
(vv) nucleotide 15589 wherein N is G;
(ww) nucleotide 15769 wherein N is T;
(xx) nucleotide 15839 wherein N is G;
(yy) nucleotide 16148 wherein N is A;
(zz) nucleotide 16198 wherein N is G; and
(aaa) nucleotide 16202 wherein N is T;
or the complement thereof.

40. The isolated nucleic acid probe of claim 39 comprising at least two of:
(a) nucleotide 701 wherein N is C;
(b) nucleotide 716 wherein N is G;
(c) nucleotide 732 wherein N is C;
(d) nucleotide 1293 wherein N is G;
(e) nucleotide 1322 wherein N is G;
(f) nucleotide 1379 wherein N is C;
(g) nucleotide 1590 wherein N is T;
(h) nucleotide 1688 wherein N is G;
(i) nucleotide 2401 wherein N is G;
(j) nucleotide 2429 wherein N is A;
(k) nucleotide 2488 wherein N is T;
(l) nucleotide 2594 wherein N is T;
(m) nucleotide 2618 wherein N is A;
(n) nucleotide 3083 wherein N is A;
(o) nucleotide 3125 wherein N is A;
(p) nucleotide 3212 wherein N is T;
(q) nucleotide 3619 wherein N is A;
(r) nucleotide 3635 wherein N is A;
(s) nucleotide 4256 wherein N is A;
(t) nucleotide 4898 wherein N is G;
(u) nucleotide 5006 wherein N is T;
(v) nucleotide 5062 wherein N is A;
(w) nucleotide 5167 wherein N is A;
(x) nucleotide 11069 wherein N is G;
(y) nucleotide 11238 wherein N is T;
(z) nucleotide 11293 wherein N is G;
(aa) nucleotide 11422 wherein N is C;
(bb) nucleotide 11686 wherein N is T;
(cc) nucleotide 12598 wherein N is C;
(dd) nucleotide 13171 wherein N is C;
(ee) nucleotide 13298 wherein N is A;
(ff) nucleotide 13645 wherein N is C;
(gg) nucleotide 13751 wherein N is A;
(hh) nucleotide 13782 wherein N is C;

(ii) nucleotide 13806 wherein N is C;
(jj) nucleotide 13813 wherein N is C;
(kk) nucleotide 14479 wherein N is G;
(ll) T is inserted after nucleotide 14546;
(mm) nucleotide 14585 wherein N is T;
(nn) nucleotide 14729 wherein N is A;
(oo) nucleotide 14787 wherein N is T;
(pp) nucleotide 14795 wherein N is A;
(qq) nucleotide 15041 wherein N is C;
(rr) nucleotide 15343 wherein N is A;
(ss) nucleotide 15449 wherein N is A;
(tt) nucleotide 15502 wherein N is A;
(uu) nucleotide 15545 wherein N is T;
(vv) nucleotide 15589 wherein N is G;
(ww) nucleotide 15769 wherein N is T;
(xx) nucleotide 15839 wherein N is G;
(yy) nucleotide 16148 wherein N is A;
(zz) nucleotide 16198 wherein N is G; and
(aaa) nucleotide 16202 wherein N is T;
or the complement thereof.

41. The probe of claim 39 comprising no more than 500 contiguous nucleotides of SEQ ID NO:8.

42. The probe of claim 39 comprising no more than 200 contiguous nucleotides of SEQ ID NO:8.

43. The probe of claim 39 comprising no more than 100 contiguous nucleotides of SEQ ID NO:8.

44. The probe of claim 39 comprising no more than 50 contiguous nucleotides of SEQ ID NO:8.

45. The probe of claim 39 comprising DNA.

46. The probe of claim 39 comprising a peptide nucleic acid.

47. The probe of claim 39 further comprising a detectable label.

48. The probe of claim 47 wherein the detectable label is a fluorescent label.

49. A method comprising:
(a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient;

(b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:8, the probe comprising at least one of:

(i) nucleotide 701 wherein N is C;
(ii) nucleotide 716 wherein N is G;
(iii) nucleotide 732 wherein N is C;
(iv) nucleotide 1293 wherein N is G;
(v) nucleotide 1322 wherein N is G;
(vi) nucleotide 1379 wherein N is C;
(vii) nucleotide 1590 wherein N is T;
(viii) nucleotide 1688 wherein N is G;
(ixi) nucleotide 2401 wherein N is G;
(x) nucleotide 2429 wherein N is A;
(xi) nucleotide 2488 wherein N is T;
(xii) nucleotide 2594 wherein N is T;
(xiii) nucleotide 2618 wherein N is A;
(xiv) nucleotide 3083 wherein N is A;
(xv) nucleotide 3125 wherein N is A;
(xvi) nucleotide 3212 wherein N is T
(xvii) nucleotide 3619 wherein N is A;
(xviii) nucleotide 3635 wherein N is A;
(xix) nucleotide 4256 wherein N is A;
(xx) nucleotide 4898 wherein N is G;
(xxi) nucleotide 5006 wherein N is T;
(xxii) nucleotide 5062 wherein N is A;
(xxiii) nucleotide 5167 wherein N is A;
(xxiv) nucleotide 11069 wherein N is G;
(xxv) nucleotide 11238 wherein N is T;
(xxvi) nucleotide 11293 wherein N is G;
(xxvii) nucleotide 11422 wherein N is C;
(xxviii) nucleotide 11686 wherein N is T;
(xxix) nucleotide 12598 wherein N is C;
(xxx) nucleotide 13171 wherein N is C;
(xxxi) nucleotide 13298 wherein N is A;
(xxxii) nucleotide 13645 wherein N is C;
(xxxiii) nucleotide 13751 wherein N is A;
(xxxiv) nucleotide 13782 wherein N is C;
(xxxv) nucleotide 13806 wherein N is C;
(xxxvi) nucleotide 13813 wherein N is C;
(xxxvii) nucleotide 14479 wherein N is G;
(xxxviii) T is inserted after nucleotide 14546;
(xxxix) nucleotide 14585 wherein N is T;
(xl) nucleotide 14729 wherein N is A;
(xli) nucleotide 14787 wherein N is T;
(xlii) nucleotide 14795 wherein N is A;

(xliii) nucleotide 15041 wherein N is C;
(xliv) nucleotide 15343 wherein N is A;
(xlv) nucleotide 15449 wherein N is A;
(xlvi) nucleotide 15502 wherein N is A;
(xlvii) nucleotide 15545 wherein N is T;
(xlvii) nucleotide 15589 wherein N is G;
(xlix) nucleotide 15769 wherein N is T;
(l) nucleotide 15839 wherein N is G;
(li) nucleotide 16148 wherein N is A;
(lii) nucleotide 16198 wherein N is G; and
(liii) nucleotide 16202 wherein N is T

or the complement thereof; and

(c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.--

REMARKS

The amendment to the specification is made solely to insert the Sequence Listing and SEQ ID NOS. into the specification. No new matter is introduced. The accompanying declaration by the inventor confirms that the sequences in the Sequence Listing are the same as those incorporated by reference into the original specification by providing the GenBank® Accession Number for each sequence. A signed declaration will be filed under separate cover.

Applicant requests that claims 17-49 be examined together without restriction. Each of SEQ ID NOs:6, 7, and 8 relate to the human thymidylate synthetase gene. SEQ ID NO:6 corresponds to the coding region. SEQ ID NO:7 correponds to the promoter region. SEQ ID NO:9 corresponds to the exons. Three SEQ ID NOs are required even though only one gene is referenced because the original specification identified the sequences by providing three GenBank® Accession Numbers.

Each of the nucleotides specified in the claims represents a single nulceotide polymorphism in the human thymidylate synthetase gene.

Attached is a marked-up version of the changes being made by the current amendment.

Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 24 Sept 2001

Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20238832.doc

Version with markings to show changes made

In the specification:

The paragraph beginning at page 1, line 8, has been amended as follows:

This application is a divisional of U.S. Application Serial No. 09/658,659, filed September 8, 2000, which is a CIP of Stanton, U.S. Application serial No. 09/596,033, filed June 15, 2000 entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application 09/357,743, filed July 20, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application Serial No. 09/357,024, filed July 19, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which claims the benefit of Stanton, U.S. Provisional Application 60/093,484, filed July 20, 1998, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which are all hereby incorporated by reference in their entireties including drawings and tables.

Table 10 beginning at page 171 has been amended as follows:

Table 10

Variance Table

Hugo Variance	GID Start	OMIM ID Variance	VGX Symbol	Description
U73338	U73338	156570	GEN-69	Methionine Synthase (SEQ ID NO:1)
	194	(-201)C>G		5'
	284	(-111)C>T		5'
	1136	742G>A		V248M
	1252	858C>T		Silent

	1334	940G>A	D314N	
	1699	1305T>C	Silent	
	3150	2756A>G	D919G	
	3207	2813G>T	S938I	
	3209	2815G>C	G939R	
	5444	5050C>A	3'	
	5551	5157G>A	3'	
	5573	5179C>T	3'	
	5659	5265T>C	3'	
	5678	5284T>C	3'	
	5874	5480C>T	3'	
	5934	5540A>G	3'	
D78586	D78586	114010	GEN-BR	CAD PROTEIN (SEQ ID NO:2)
	3434	3408C>T	Silent	
	4313	4287T>C	Silent	
	4799	4773A>G	Silent	
	5255	5229C>T	Silent	
	5455	5429G>A	R1810Q	
	5507	5481T>C	Silent	
	5810	5784C>T	Silent	
	6128	6102C>T	Silent	
	6626	6600C>T	Silent	
	6686	6660C>T	Silent	
U09178	U09178	274270	GEN-HA	Dihydropyrimidine Dehydrogenase (SEQ ID NO:3)
	166	85T>C	C29R	
	577	496A>G	M166V	
	638	557A>G	Y186C	
	1708	1627A>G	I543V	
	3432	3351T>C	3'	
	3682	3601C>T	3'	
	3730	3649G>A	3'	
	3925	3844A>G	3'	
	3937	3856T>C	3'	
U19720	U19720	600424	GEN-I1	Folate Transporter (SLC19A1) (SEQ ID NO:4)
	175	80G>A	R27H	
	341	246C>G	Silent	
	791	696C>T	Silent	
	1067	972G>A	Silent	
	1337	1242C>A	Silent	
	1997	1902T>C	3'	
	2100	2005^2006insG	3'	
	2582	2487T>G	3'	

	2617	2522C>T		3'
	2652	2557T>C		3'

U92868 U92868 600424 GEN-LUK Homo sapiens reduced folate carrier (RFC1) gene, exons 1a, 1c and 1b (SEQ ID NO:5)

431	431A>G	Intron	
441	441A>G	Intron	
498	498C>T	Intron	
579	579G>C	Intron	
599	599G>C	Intron	

X02308 X02308 188350 GEN-KL Thymidylate synthetase (SEQ ID NO:6)

1066	961T>C		3'
1136	1031A>G		3'
1497	1392T>A		3'

D00517 D00517 188350 GEN-LUC Thymidylate synthase, promoter (SEQ ID NO:7)

276	276C>T	Intron	
321	321T>C	Intron	
452	452G>A	Intron	
457	457^insC	Intron	
491	491C>A	Intron	
533	533T>C	Intron	
624	624A>C	Intron	
639	639A>G	Intron	
655	655T>C	Intron	

D00596 D00596 188350 GEN-LUD Homo sapiens gene for thymidylate synthase, exons 1, 2, 3, 4, 5, 6, 7, complete cds (SEQ ID NO:8)

701	701A>C	Intron	
716	716A>G	Intron	
732	732T>C	Intron	
1293	1293A>G	Intron	
1322	1322C>G	Intron	
1379	1379T>C	Intron	
1590	1590C>T	Intron	
1688	1688C>G	Intron	
2401	2401A>G	Intron	
2429	2429G>A	Intron	
2488	2488C>T	Intron	
2594	2594G>T	Intron	
2618	2618G>A	Intron	
3083	3083G>A	Intron	
3125	3125G>A	Intron	
3212	3212C>T	Intron	
3619	3619T>A	Intron	

	3635	3635G>A	Intron
	4256	4256G>A	Intron
	4898	4898A>G	Intron
	5006	5006C>T	Intron
	5062	5062G>A	Intron
	5167	5167G>A	Intron
	11069	11069A>G	Intron
	11238	11238C>T	Intron
	11293	11293T>G	Intron
	11422	11422T>C	Intron
	11686	11686C>T	Intron
	12598	12598T>C	Intron
	13171	13171T>C	Intron
	13298	13298G>A	Intron
	13645	13645T>C	Intron
	13751	13751C>A	Intron
	13782	13782T>C	Intron
	13806	13806T>C	Intron
	13813	13813T>C	Intron
	14479	14479A>G	Intron
	14546	14546^insT	Intron
	14585	14585C>T	Intron
	14729	14729G>A	Intron
	14787	14787C>T	Intron
	14795	14795G>A	Intron
	15041	15041T>C	Intron
	15343	15343G>A	Intron
	15449	15449G>A	Intron
	15502	15502G>A	Intron
	15545	15545C>T	Intron
	15589	15589A>G	Intron
	15769	15769C>T	3'
	15839	15839A>G	3'
	16148	16148G>A	3'
	16198	16198T>G	3'
	16202	16202G>T	Intron
X59618	X59618	180390	GEN-M3 Ribonucleotide reductase M2 polypeptide (SEQ ID NO:9)
	128	(-67)G>A	5'
	189	(-6)T>G	5'
	524	330C>G	Silent
	1399	1205T>A	3'
	1464	1270G>A	3'
	1636	1442C>T	3'
	1738	1544C>T	3'

	2259	2065T>C		3'
S72487	S72487	131222	GEN-3LD	Thymidine phosphorylase, partial (SEQ ID NO:10)
	183	19G>A		D7N
	483	319C>T		3'
	601	437G>C		3'
	1299	1135G>A		3'
M58602	M58602	131222	GEN-LUB	Thymidine phosphorylase, promoter and genomic (SEQ ID NO:11)
	124	124C>T		3'
	439	439G>A		3'
	1044	1044^insCT		3'
	1331	1331G>A		3'
	1977	1977G>A		Intron
	2149	2149G>A		Intron
	2467	2467A>G		Intron
	2634	2634C>G		Intron
	2975	2975G>A		Intron
	3116	3116G>T		Intron
	3255	3255A>C		Intron
	3344	3344T>C		Intron
	4051	4051C>A		Intron
	4782	4782G>A		Intron
	5022	5022T>C		Intron
	5266	5266G>A		Intron
	5285	5285C>G		Intron
	5438	5438T>A		Intron
	5482	5482C>T		Intron
	5629	5629G>A		Intron
	5648	5648C>T		Intron
	5731	5731G>A		Intron
M98045	M98045	136510	GEN-4C3	Homo sapiens folylpolyglutamate synthetase mRNA, complete cds (SEQ ID NO:12)
	802	732C>T		Silent
	1747	1677G>T		3'
	1900	1830T>C		3'
U24253	U24253	136510	GEN-LUE	Human folylpolyglutamate synthetase (FPGS) gene, exons 5-11, and partial cds (SEQ ID NO:13)
	1424	1424C>A		Intron
	1649	1649G>A		Intron
	2554	2554A>G		Intron
U24252	U24252	136510	GEN-LUF	Folylpolyglutamate synthetase, promoter and exons 1-4 (SEQ ID NO:14)

263	263A>G	Intron	
266	266G>T	Intron	
527	527C>G	Intron	
1037	1037A>G	5'	
1139	1139G>A	Intron	
1217	1217C>T	Intron	
1647	1647C>T	Intron	
1955	1955G>A	Intron	
2017	2017G>A	Intron	
2037	2037G>A	Intron	
2189	2189A>G	Intron	
2282	2282C>T	Intron	
2309	2309A>G	Intron	

U09806 U09806 236250 GEN-4FZ Human methylenetetrahydrofolate reductase mRNA, partial cds (SEQ ID NO:15)

120	120T>C	Silent	
464	464T>G	M155R	
519	519C>T	Silent	
668	668C>T	A223V	
1059	1059T>C	Silent	
1289	1289C>A	3'	
1308	1308T>C	3'	
1784	1784G>A	3'	

AF061655 AF061655 123920 GEN-LUJ Cytidine deaminase, promoter (SEQ ID NO:16)

575	575T>C	Intron	
648	648T>C	Intron	
771	771G>C	Intron	
883	883G>A	Intron	
941	941^insC	5'	
1051	1051A>C	K27Q	